II. REMARKS

Formal Matters

Claims 1, 2, 4-12, 20-22, 24-28, 40, and 42-45 are pending after entry of the amendments set forth herein.

Claims 1-35 and 39-41 were examined and were rejected. Claims 36-38 were withdrawn from consideration.

Claims 1, 7, 20, and 26 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Claims 7 and 26 were amended to change the claim dependency. Support for the amendments to claims 1 and 20 is found in the claims as originally filed, and throughout the specification, in particular at the following locations: Example 1; page 14, lines 11-20; and Figures 1 and 2. Accordingly, no new matter is added by these amendments.

Claims 3, 13-19, 23, 29-39 and 41 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

New claims 42-45 are added. New claims 42-45 contain language recited in original claims 7-10. Accordingly, no new matter is added.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Examiner Interview

The undersigned Applicants' representative wishes to thank Examiner Hayes for the courtesy of a telephonic interview, which took place on August 14, 2003. During the telephonic interview, the rejections of certain claims under 35 U.S.C.§112, first paragraph, were discussed. Possible claim amendments were discussed. The claim amendments and arguments presented herein reflect the discussions.

Information Disclosure Statement

The Office Action stated that the Information Disclosure Statement (IDS) filed on July 9, 2002 fails to comply with 37 C.F.R.§1.98(a)(2).

The Office Action indicated that no copy of WO 91/03568 was provided. However, a copy of WO 91/03568 was provided on a compact disc along with the response filed on July 9, 2002. Nevertheless, a further copy of WO 91/03568 is provided herewith.

Rejections withdrawn

Applicants note with gratitude that the following rejections, made in the Office Action mailed February 13, 2002, have been withdrawn: 1) rejection of claims 1-35 under 35 U.S.C.§101 and 35 U.S.C.§112, first paragraph; and 2) rejection of claims 1-35 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C.§112, first paragraph

Claim 40 was rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking written description. Claims 1-35 and 39-41 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement.

Claim 40; written description

The Office Action stated that no proper antecedent basis nor conception in context with that described in the specification at the time of filing is apparent for the recitation "active fragment thereof."

However, the specification states: "factors which are useful in practicing this invention include one or more neurotrophic factor such as brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4) **or functional derivatives or analogs thereof**." Specification, page 8, lines 4-7. The specification further states that a functional derivative of a factor is a compound which is an analog **or an active fragment** of the compound or its analog. Specification, page 8, lines 13-15. Thus, the specification provides adequate written description for the phrase "active fragment thereof." Accordingly, claim 40 need not be amended.

Claims 1-35 and 39-41; enablement

The Office Action stated that the specification does not reasonably provide enablement for any method of reducing neurodegeneration of retinal neurons generically with structurally and functionally uncharacterized modified neurotrophic factors/fragments, orally, subcutaneously, intravenously, or intramuscularly. Applicants respectfully traverse the rejection.

Claims 13-19, 29-35, 39, and 41 are canceled without prejudice to renewal, thereby rendering the rejection of these claims moot. Applicants respectfully traverse the rejection of claims 1-12, 20-28, and 40.

Neurotrophic factors

The Office Action stated that the specification is enabling for a method of reducing degeneration of the outer segment of photoreceptor cells following intraocular or systemic administration of BDNF, CNTF, NT-3, aFGF, bFGF, IL-1β, TNF-α, and IGF-2. As discussed in the amendment, filed on July 9, 2002 and responsive to the February 13, 2002 Office Action, the specification provide a description of how to determine whether a given neurotrophic factor reduces retinal cell degeneration, and provides working examples of eight different factors that were effective in reducing degeneration of the retinal cells such as photoreceptors. The Office Action stated that Applicants' arguments are persuasive concerning enabling use of "neurotrophic factors" for "rescue of photoreceptors."

The Office Action stated that "active fragments thereof" are not enabled for reasons of record, and consistent with the teachings of Rudinger previously made of record. The February 13, 2002 Office Action stated that Rudinger teaches that it is impossible to attach a unique significance to any residue in a sequence, and that Rudinger teaches that the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study.

However, Rudinger discusses the hormone oxytocin and amino acid changes that can affect receptor binding etc. Rudinger does not discuss fragments of neurotrophic factors that reduce degeneration of a retinal neuron, and how to determine whether such fragments are active in reducing degeneration of a retinal neuron. Accordingly, Rudinger does not support a rejection of the instant claims based on an alleged lack of enablement.

Furthermore, Rudinger was published in 1976, while the instant application has a priority date of 1989. The skill level of those of ordinary skill in the art with respect to generating fragments of a given neurotrophic factor and testing the activity of same was higher is 1989 than it was in 1976. Accordingly, Rudinger does not support a rejection of the instant claims based on an alleged lack of enablement.

Still further, as noted above and previously, the specification teaches exactly how to determine whether a given neurotrophic factor is active in reducing degeneration of a retinal cell such as a photoreceptor. The specification provides eight examples of different neurotrophic factors that reduce degeneration of a retinal cell such as a photoreceptor. Preparation of fragments of any given neurotrophic factor is a routine matter involving nothing more than the skills of a laboratory technician. Testing of such fragments is also routine, given the level of skill in the art and the guidance provided in the specification. Accordingly, the specification is enabling for the full scope of the claims.

Routes of administration

The Office Action stated that the instant specification does not reasonably provide enablement for any route of administration.

Applicants' position on the enablement of various routes of administration has been previously made of record, e.g., in the amendment, filed on July 9, 2002 and responsive to the February 13, 2002 Office Action, and is not reiterated herein. It is Applicants' position that the specification is enabling for the full scope of the claims.

Nevertheless, and solely in the interest of expediting prosecution, claims 1 and 20 are amended to recite "wherein said administration is intraocular or systemic." The instant specification indicated that the specification is enabling for intraocular and systemic administration.

Retinal neurons

The Office Action stated that the specification is not enabling for reducing degeneration of retinal neurons other than photoreceptors, consistent with the teachings of Rapp, the Merck Manual, and Jackowski previously made of record. Applicants respectfully traverse the rejection.

Retinal neurons

The specification states that the invention provides methods for reducing degeneration of various retinal cells, including photoreceptors, retinal ganglion cells, displaced retinal ganglion cells, amacrine cells, displaced amacrine cells, and horizontal and bipolar neurons. Specification, page 7, lines 16-21. Applicants have provided working examples of reduction of degeneration of photoreceptors. Example 1. Those skilled in the art would reasonably expect that the instant methods as claimed are effective to reduce degeneration of retinal neurons in addition to photoreceptors.

The fact that those skilled in the art would reasonably expect that the instant methods as claimed are effective to reduce degeneration of retinal neurons is corroborated by the following references, copies of which were provided in the amendment, filed on July 9, 2002 and responsive to the February 13, 2002 Office Action:

1) Peterson et al. (2000) *J. Neurosci.* 20:4081-4090;

Peterson et al. states that CNTF enhances survival of retinal ganglion and photoreceptor cells exposed to otherwise lethal perturbation.

2) Kido et al. (2000) *Brain Res.* 884:59-67;

Kido et al. discuss the ability of BDNF to protect inner retinal cells, retinal ganglion cells, and amacrine cells from N-methyl-D-aspartate-induced neuronal death.

3) Chen and Weber (2001) *Invest. Ophthamol. Vis. Sci.* 42:966-974;

Chen and Weber discuss the ability of BDNF to enhance retinal ganglion cell survival.

4) Schmeer et al. (2002) *Eur. J. Neurosci.* 15:637-643;

Schmeer et al. discusses the ability of GDNF to enhance retinal ganglion cell survival.

Thus, the instant methods as claimed are enabling for methods of reducing degeneration of retinal neurons. The art cited in the August 27, 1999 Office Action (which was in any case vacated) does not support a rejection on the basis of alleged lack of enablement. Neither Rapp nor Jackowski supports the contention that the instant methods are not enabled for reducing degeneration of any retinal neuron. The August 27, 1999 Office Action stated that only the outer segment of photoreceptor cells can effectively be treated when damaged, citing Rapp, page 971, Figure 2. However, Figure 2 of Rapp

does not teach that only the outer segment of photoreceptor cells can be effectively treated when damaged. Accordingly, Rapp does not support the contention that the instant methods are not enabled for reducing degeneration of any retinal neuron. Jackowski does not relate to reducing degeneration of retinal neurons. Instead, Jackowski relates to CNS regeneration. Accordingly, Jackowski does not support the contention that the instant methods are not enabled for reducing degeneration of any retinal neuron.

Nevertheless, and solely in the interest of expediting prosecution, claims 1 and 20 are amended to recite "reducing degeneration of a photoreceptor."

Conclusion as to the rejections under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1-35 and 39-41 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.